REMARKS/ARGUMENTS

Claims 1-10, 20-25 and 27-44 are pending. Claims 11-19 and 26 were previously canceled without prejudice or disclaimer of the subject matter they contain. It is believed that no new matter has been introduced. Applicants do not acquiesce to the propriety of any of the Examiner's rejections and do not disclaim any subject matter to which Applicants are entitled. *Cf. Warner Jenkinson Co. v. Hilton-Davis Chem. Co.,* 41 U.S.P.Q.2d 1865 (U.S. 1997). Further, Applicants reserve the right to file continuing applications to cover disclosed subject matter not encompassed by the currently pending claims.

REJECTION UNDER 35 U.S.C. § 103

The Office Action rejects claims 1-10, 20-25 and 27-44, under 35 U.S.C. § 103(a) as allegedly being unpatentable over **Doi** (FEBS Letters, 457:227-230 (1999)) in view of **Praszkier** (J. Bacteriol., 181:2765-2772 (1999)). Applicants respectfully traverse this rejection.

"Before a conclusion of obviousness may be made based on a combination of references, there must have been a reason, suggestion, or motivation to lead an inventor to combine those references." *Pro-Mold and Tool Co. v. Great Lakes Plastics Inc.*, 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996). "[E]vidence of a motivation to combine [references] need not be found in the prior art references themselves, but rather may be found in 'the knowledge of one of ordinary skill in the art or, in some cases, from the nature of the problem to be solved.'" *Dystar Textilfarben Gmbh v. C.H. Patrick Co.*, 464 F.3d 1356, 1366, 80 USPQ2d 1641, 1649 (Fed. Cir. 2006) (emphasis in original, quoting *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999)). However, "...rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." (*In re Kahn*, 441 E

3d 977, 988 (CA Fed. 2006). Applicants cannot overemphasize that the Office Action has not discharged the USPTO's initial burden of providing a basis upon which to predicate the legal conclusion that one having ordinary skill in the art would have considered the claimed invention obvious over the applied references.

As will be explained in further detail below, Applicants respectfully submit that Doi essentially teaches a method for producing *in vitro* libraries but does not describe any cis-acting proteins. Praszkier fails to remedy the deficiencies of Doi. Praszkier merely teaches the so-called repA/ori system, but does not teach or suggest any particular practical or commercial use for such a system. One of ordinary skill in the art reading Doi would have had no reason to consult Praszkier to try DNA binding proteins other than those described by Doi. Moreover, Praszkier does not teach or suggest that the repA/ori system could be modified to produce an *in vitro* peptide expression library, as presently claimed. Further, Praszkier nowhere suggests that the repA/ori system might be applicable to the type of methods described by Doi. There simply is no teaching, suggestion, motivation or expectation of success in Praszkier to combine its teachings with Doi, to obtain a method, as currently claimed.

The abstract of the Doi paper describes a method that permits the *in vitro* construction and selection of peptide or protein libraries. Doi has named the disclosed method as the "STABLE," which stands for "STA-biotin linkage in emulsions":

> *"This method relies on an in vitro transcription/translation reaction compartmentalized in water in oil emulsions. In each emulsion compartment, streptavidin (STA)-fused polypeptides are synthesized and attached to the encoding DNA via its biotin label. The resulting protein-DNA fusion molecules recovered from the emulsion can be subjected to affinity selection based on the properties of the peptide portion, whose sequence can be determined from that of its DNA-tag".*

One of ordinary skill in the art reading Doi as a whole would readily recognize that there are certain key features of the disclosed method that are distinguishable from the claimed invention, namely:

- The Doi method relies on compartmentalization in a water-in-oil emulsion during the transcription/translation reaction.
- The Doi method utilizes binding between streptavidin attached to the polypeptide and biotin attached to the DNA.
- Only after the transcription/translation reaction has been carried out and the streptavidin-fused polypeptide has been attached to the encoding DNA via its biotin label can the fusion molecules be recovered from the emulsion.

As defined in claim 1, the DNA construct of the claimed invention comprises a DNA target sequence to which a peptide encoded by the DNA construct will non-covalently bind. In contrast, Doi does not include a DNA target sequence in the DNA molecules. Rather, the disclosed DNA molecules are tagged using a biotin label. Streptavidin fused to the polypeptide of interest does not bind to the DNA molecule itself, but only attaches indirectly via the biotin label.

Further, Doi (like the previously mis-applied Schatz reference) conspicuously teaches that the disclosed method must be carried out in a compartmentalized system. As is clear from its name, the "STABLE" system described by Doi requires compartmentalization in a water in oil emulsion. The streptavidin-biotin binding described by Doi can only be used in such a compartmentalized system.

In order to achieve specific binding of a polypeptide only to its encoding DNA, one of ordinary skill in the art would readily recognize that it is necessary to compartmentalize the different DNA molecules in separate compartments within the emulsion when carrying out the transcription/translation reaction. Expression of each DNA is carried out in a separate compartment in the emulsion because the streptavidin on the expressed polypeptide can bind to any biotin that is present. By expressing only a single type of DNA in each compartment, the polypeptide expressed in that compartment is only able to bind to the encoding DNA, since that is the only DNA (and the only biotin) that is present. As explained in the last sentence of the "Introduction" of Doi, the streptavidin-biotin linkage is very strong once formed. In other words, after protein and DNA have been fused by the streptavidin-biotin binding, the fusion molecules can then be recovered and mixed together to form a library, retaining the existing binding, and therefore the existing specificity.

However, if more than one encoding DNA is expressed in the same compartment using the Doi method, the expressed streptavidin-fused polypeptides could bind to any biotin labelled DNA molecule in the same compartment. That is, there would no longer be any specificity of binding here. Any streptavidin-protein molecule could bind to any DNA-biotin molecule in the same compartment. After transcription and translation have been achieved and streptavidin-biotin binding has occurred within each compartment of the emulsion, the molecules can be extracted from the emulsion and mixed.

In contrast, the claimed invention employs cis-acting DNA binding proteins and allows the concurrent production of multiple peptide-DNA conjugates in a single acellular environment or, for example, a single compartment. By using a cis-acting system such as the RepA-ori system exemplified in the specification, the claimed method achieves binding specificity, even

where multiple different DNA constructs are expressed in the same solution or compartment. According to the claimed invention, each expressed polypeptide will bind only to its encoding DNA molecule, even if other DNA molecules having the same target sequence are also present. This binding specificity could not be achieved without compartmentalization using the approach described by Doi.

The claimed method could not be achieved by following the teaching of Doi. Furthermore, in following the teaching of Doi, the skilled reader would actually be led away from the present invention because Doi is specifically directed to the use of emulsions for this purpose. In particular, Doi teaches that emulsions are particularly advantageous because they allow the compartmentalization of different polypeptides and therefore allow this specific binding. Doi discusses earlier methods, such as methods in which compartmentalization was achieved by expression in separate cells, and teaches that an emulsion-based approach is an alternative way of producing protein-DNA libraries.

The approach claimed in the present case, which does not even require compartmentalization, is radically different from that described by Doi. Doi highlights the advantages of its emulsion based system and it is clear that the whole purpose of the "STABLE" system described by Doi is to allow production of suitable protein-DNA fusion molecules in such an emulsion based system. Applicants contend that one of ordinary skill in the art reading Doi would therefore have no reason to try to develop a different system, as claimed, where such an emulsion is not required. Furthermore, the "STABLE" system described in Doi specifically requires streptavidin-biotin linkage. This is even inherent in the name of the system. As explained above, a system based on streptavidin-biotin binding will not achieve the specificity achieved/required by the claimed invention. Any streptavidin can bind to any biotin and there is

no suggestion in Doi of any approach (other than compartmentalization) that could be used to ensure specific binding to a particular DNA-biotin.

Moreover, the Office Action has suggested that Doi teaches that "*many other DNA binding proteins could also be used as adaptors for the protein-DNA linkage*". Presumably, the Office Action is referring to the first full sentence at page 229, right hand column of Doi, which states:

> *"In this study, we used STA as a fusion partner of the random peptide library, but many other proteins (e.g. DNA binding proteins [8]) could also be used as adaptors for the protein-DNA linkage".*

First, Doi teaches that this STA-biotin system is particularly preferred because the binding between STA and biotin is very stable, "*virtually equivalent to a covalent bond*" (see the last sentence of the "Introduction" in Doi). An ordinary skilled artisan who might have been contemplating modifications to the approach described in Doi would therefore have been cautious in trying to select an alternative approach due to the particular features described for the STA-biotin system.

Second, the sentence quoted above referring to other DNA binding proteins makes specific reference to document [8] cited in the Doi paper. Reference [8] is a paper by Cull (1992). That document was submitted by the Applicants in the Information Disclosure Statement of March 4, 2005, and describes a system for generating peptide libraries making use of the specific binding of lac-repressor protein (LacI) to the lac-repressor binding site. That system was used to construct libraries of peptides wherein each peptide was linked to the genetic material encoding it.

The proteins used in the methods of Cull do not have cis-acting binding protein activity as required by claim 1. The system described in Cull is therefore not a system as required by claim 1 of the present application. As with the Doi method, in order to generate a peptide display library using the DNA binding protein described in Cull, it would be necessary to express each of the DNA molecules separately. There is no specificity of binding using such a method that would ensure that an expressed protein would bind only to the particular DNA molecule that encoded it. If a plurality of different DNA molecules as described in Cull were simultaneously expressed, there would be no way of guaranteeing that each expressed peptide would be linked only to the DNA molecule that encoded it. Rather, one would expect different peptides to randomly bind to different DNA molecules within the mixture.

Applicants respectfully submit that one of ordinary skill in the art would recognize that the DNA binding proteins described by Cull are therefore also not suitable for use in the claimed method. They may form a suitable alternative to the streptavidin-biotin system described by Doi since they would probably be effective in a method carried out in a compartmentalized system such as the emulsion system described by Doi. However, neither the streptavidin-biotin binding described by Doi or the lac-repressor binding system described by Cull would be effective in a method as presently claimed.

Doi therefore teaches alternative DNA binding protein systems that could be used in place of the streptavidin-biotin binding in its preferred method. However, those alternative systems will also require the compartmentalization that is essential to the Doi approach. There is nothing in Doi that would have reasonably lead the skilled reader to a system, as presently claimed, which employs a cis-acting binding protein, and which allows claimed method step (b) to be carried out, wherein a plurality of DNA constructs are expressed together such that each

expressed peptide is non-covalently bound specifically to the DNA molecule from which it was produced, rather than to other DNA molecules in the same solution. Moreover, there is nothing in Doi that would lead the skilled reader to try to develop a non-compartmentalized system.

Rather, the entire purpose of Doi is to develop a suitable emulsion based system that allows for specificity of binding by compartmentalizing the individual molecules. Based on the teaching of that system, the skilled reader would be led away from developing a system that did not require such compartmentalization and that did not require such an emulsion. Rather, the general reference on page 229 of Doi to *"other proteins, e.g. DNA binding proteins"* would be clearly understood by one of ordinary skill in the art as referring to other DNA binding proteins that could be used in a similar compartmentalized system, such as the lac-repressor protein described in Cull.

Whether alone or improperly combined, none of the cited or applied documents purportedly relating to protein libraries in which polypeptides are bound to their encoding DNA molecules actually teaches or suggests that a cis-acting system, as now claimed, might have any advantages. Applicants assert that there is nothing in any of the cited documents that would lead one of skill in the art to consider using such a cis-acting system in the production of protein-DNA libraries. Rather, all the documents cited by the Examiner are directed to particular alternative solutions to this problem, that use, for example, water in oil emulsions or cell-based systems, in order to compartmentalize the DNA being expressed and to ensure that the expressed protein is able to bind only to its encoding DNA molecule.

"[One] cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988)). The inappropriateness of hindsight as a test of obviousness was, in point of fact

discovered, and articulated lucidly, over three centuries ago, by Milton, who, in *Paradise Lost, Part IV*, L. 478-501, stated:

> *The invention all admired, and each how he*
> *To be the inventor missed; so easy it seemed,*
> *Once found, which yet unfound most would have thought,*
> *Impossible!*

The mere fact that the prior art may be modified in the manner suggested by the Office Action is not enough to have made the alleged modifications obvious unless the applied references suggested the desirability of the modification. *In re Fritch*, 23 U.S.P.Q.2d 1780, 1783-84 (Fed. Cir. 1992). The bottom line is that the combination of the Doi with the Praszkier is considered to be result of hindsight. Praszkier describes the RepA/ori system but makes no suggestion at all that such a system could be used in generating protein libraries. Doi provides no suggestion or expectation of success in selecting select such a system in preference to any of the multitude of other DNA binding proteins available in the art at the time the claimed invention was made. Doi nowhere suggests that the DNA binding protein described by Praszkier might have any particular advantages or utility. Indeed, if the DNA binding protein described by Praszkier was used in the emulsion based described by Doi, it would not be expected to have such advantages. The use of an emulsion to separate the different DNAs and to allow specific binding of expressed proteins to their encoding DNAs would make the use if a cis-acting protein unnecessary. The advantages of the cis-acting systems currently claimed is that they allow expression of multiple DNA molecules to be carried out at the same time without the need to compartmentalize them as required in the emulsion system described by Doi. In view of the above, reconsideration and withdrawal of this rejection are respectfully requested.

CONCLUSION

If anything further could be done to place the above-captioned patent application in better condition for allowance (i.e., via Examiner's Amendment), then please contact the undersigned attorney at the telephone number listed below.

Applicants hereby request any extension of time deemed necessary for entry of this submission and any submission filed hereafter in this application or any continuing application(s). Applicants make a Conditional Petition for any relief available to correct any defect in connection with this filing, or any defect remaining in this application after this filing. The Commissioner is authorized to charge any petition fee or any deficiency in fees filed, or asserted to be filed, or which should have been filed herewith (or with any paper filed hereafter) to Deposit Account No. **14-1140 (please use reference number: WFG-117-533)** or credit any overpayment of fees to such Deposit Account.

Respectfully submitted,

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Date: May 13, 2010

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